Supplementary Table 2 **Summary of Studies Conducting Analysis of hMLH1 / hMSH2 in Colorectal Cancer Cases**

NB: The aim of this table is to summarise the findings of studies that conducted mutation analysis of hMLH1 / hMSH2 in colorectal cancer cases. Therefore, for the purpose of this table, "mutations" have been defined as those variants considered significant by the authors of the original papers.

NB: Definitions of commonly used family history criteria can be found in Appendix 1

(a) Mutation Analysis in Patients with a Family History of Colorectal Cancer

(i) Asia

Area of Study ; Recruitment period	Study Population and selection criteria	Total Number	Extent of Family History	Select Number	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
Japan	Japanese kindreds	37	Fulfilment of Amsterdam Criteria	15	1 (6.7%)	8 (53.3%)	SSCP ⇒ Sequencing	[Bai et al., 1999]
			Fulfilment of Japanese Criteria	22	0	3 (13.6%)		
Japan	Japanese families that include multiple patients with CRC	11	Fulfilment of Amsterdam Criteria	11	5 (45.5%)	0	SSCP ⇒ Sequencing	[Miyaki et al., 1995]

Japan	Unrelated patients from laboratories in Japan (n=19), Korea (n=9) and the USA (n=6)	34	Fulfilment of Amsterdam Criteria	34	8 (24%)	N / A	SSCP ⇒ Sequencing	[Han et al., 1995]
Japan	Japanese Kindreds	15	Fulfilment of Amsterdam Criteria	4	0 (Plus two missense mutations of uncertain pathogenicity)	1 (25%)	RNA ⇒ Long RT-PCR ⇒ Sequencing	[Nomura et al., 2000]
			Fulfilment of Japanese Criteria (1 group A, plus 10 group B)	11	1 (9.1%)	4 (36.4%) (Plus three missense mutations of uncertain pathogenicity)		
Korea	Kindreds registered with the Korean Hereditary Colorectal Cancer Registry as having HNPCC or suspected HNPCC.	42	Group 1: Fulfilment of Amsterdam Criteria	25	8 (32%)	0	SSCP ⇒ Sequencing	[Han et al., 1996]
			Group 2: Strong family history, but Amsterdam criteria <u>not</u> fulfilled	17	4 (23.5%) NB – see below	0		

Korea	Kindreds registered with the Korean Hereditary Colorectal Cancer Registry. NB - This study was an extension of Han et al., (1996), and includes the 17 families previously analysed	31	Strong family history, but Amsterdam criteria not fulfilled	31	5 (16.1%)	2 (6.5%)	SSCP ⇒ Sequencing	[Yuan et al., 1998]
Korea	Kindreds registered with the Korean Hereditary Colorectal Cancer Registry.	88	Fulfilment of the Amsterdam Criteria (n=33), or a history suggestive of HNPCC (n=55)	88	18 (20.5%)	2 (2.3%)	SSCP ⇒ Sequencing	[Park et al., 1999a]

(ii) Europe

Area of Study ; Recruitment period	Study Population and selection criteria	Total Number	Extent of Family History	Select Number	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
Russia / Moldavia	Kindreds from Russia (n=3) and Moldavia (n=8)	11	Group 1: Fulfilment of Amsterdam Criteria	7	1 (14.3%)	3 (42.9%)	Sequencing	[Maliaka et al., 1996]
			Group 2: Clustering of colorectal and endometrial cancer in consecutive generations	4	1 (25%)	1 (25%)		
Finland	Finnish kindreds	55	Group 1: Fulfilment of Amsterdam Criteria	35	29 (82.9%)	1 (2.9%)	RT-PCR ⇒ 2-D DNA electrophoresis ⇒ Sequencing	[Nystrom-Lahti et al., 1996]
			Group 2: An average of 4 affected members of each family, but not meeting the Amsterdam Criteria	20	5 (25%)	1 (5%)		
Sweden	Kindreds referred to the clinic for familial cancer at the Karolinska Hospital, Stockholm. Three families were of Finnish origin, while the rest were Swedish	39	Group 1: Fulfilment of Amsterdam Criteria	21	5 (23.8%)	N / A	DGGE ⇒ Sequencing	[Tannergard et al., 1995]
			Group 2: Family history of CRC	18	3 (16.7%)	N / A		

Sweden	Kindreds referred to the clinic for familial cancer at the Karolinska Hospital, Stockholm. Three families were of Finnish origin, while the rest were Swedish	39	Group 1: Fulfilment of Amsterdam Criteria	21	N / A	1 (4.8%)	DGGE ⇒ Sequencing	[Wahlberg et al., 1997]
			Group 2: Family history of CRC	18	N / A	1 (5.6%)		
Sweden	Families recruited from N. Sweden and the Stockholm region through cancer family clinics at the Karolinska Hospital and Umea University Hospital	34	Group 1: Fulfilment of Amsterdam Criteria	7	1 (14.2%)	0	DGGE ⇒ Sequencing	[Liu et al., 1998]
			Group 2: More than one member affected with CRC or associated tumours, plus four families with at least one case with onset <35 years	27	1 (3.7%)	3 (11.1%)		
Switzerland	Kindreds	10	Fulfilment of Amsterdam Criteria	10	3 (30%)	3 (30%)	Direct Sequencing	[Buerstedde et al., 1995]

Switzerland	Kindreds referred to University Hospital, Basel, from all parts of Switzerland, due to familial aggregation of CRC cases	26	Fulfilment of Amsterdam Criteria	15	6 (40%)	4 (27%)	SSCP ⇒ Sequencing	[Heinimann et al., 1999]
			Fulfilment of criteria extended to include extra-colonic tumours	11 NB - two missense alterations excluded from analysis	0	0		
Switzerland	Index cases were referred to a familial cancer clinic with suspected HNPCC	23	Group 1: Fulfilment of Amsterdam Criteria	14	10 (71.4%)	0	IVSP ⇒ Sequencing	[Hutter et al., 1998]
			Group 2: "HNPCC-like" but Amsterdam criteria not fulfilled	9	1 (11.1%)	0		
Italy	Families identified through probands hospitalised at the National Tumour Institute of Milan	16	Group 1: Fulfilment of Amsterdam Criteria	14	4 (28.6%)	3 (21.4%)	Combined strategies, including: IVSP, SSCP and direct sequencing	[Pensotti et al., 1997]
			Group 2: Strong family history, but Amsterdam criteria not fulfilled	2	0	1 (50%)		

Italy	Italian colorectal cancer patients identified through the specialised Modena CRC Registry.	36	Group 1: Fulfilment of Amsterdam Criteria	18	1 (5.6%)	2 (11.1%)	RT-PCR + SSCP ⇒ Sequencing	[de Leon et al., 1999]
			Group 2: “suspected HNPCC”, Amsterdam criteria not fulfilled.	18	0	0		
Italy	Italian kindreds	17	Fulfilment of Amsterdam Criteria	17	5 (29.4%)	2 (11.8%)	RT-PCR + SSCP ⇒ Sequencing	[Viel et al., 1997]
Italy	CRC patients identified through the Institute of Pathology and the Department of Clinical Physiopathology of the University of Florence, and from the Register of the Regina Elena Cancer Institute in Rome.	30	Group 1: Fulfilment of Amsterdam Criteria	17	2 (11.8%)	3 (17.6%)	IVSP ⇒ Sequencing	[Curia et al., 1999]
			Group 2: “HNPCC families”, but Amsterdam criteria not fulfilled	13	2 (15.4%)	0		

Italy	CRC patients. Some of these patients had previously been reported by Pensotti et al.,	45	Group 1: Fulfilment of Amsterdam Criteria	13	3 (23.1%)	3 (23.1%)	SSCP ⇒ Sequencing	[Calistri et al., 2000]
			Group 2: Incomplete HNPCC families, of patients with a strong family history, plus one patient with multiple primary tumours	11	1 (9.1%)	1 (9.1%)		
Italy, April 1994 – March 1996	CRC patients identified in three institutions – Aviano, Modena and Rome with putative HNPCC, but from families not meeting the standard Amsterdam criteria	32	At least one of the following criteria was met: - A family history suggestive of HNPCC, but one or more of the requirements of the Amsterdam criteria not fulfilled (n=29) - Age of onset < 40 years (n=15) - Multiple tumours in the index case(n=4)	32	3 (9.4%) NB - including two missense mutations of uncertain significance	3 (9.4%)	SSCP ⇒ Sequencing	[Genuardi et al., 1998]
France	CRC patients	17	Group 1: Fulfilment of Amsterdam Criteria	10	3 (30%)	2 (20%)	SSCP ⇒ Sequencing	[Dieumegard et al., 2000]
			Group 2: Strong family history, but at least one Amsterdam criterion <u>not</u> fulfilled	7	2 (28.6%)	1 (10%)		

France	Families with suspected HNPCC, after exclusion of FAP	17	- At least one family member who developed CRC at <50 years - Index patient had at least one first degree relative with CRC or a tumour in the HNPCC spectrum - At least 2 successive generations affected	17	5 (29.4%)	N / A	RT-PCR ⇒ Sequencing	[Mauillon et al., 1996]
France + Turkey	French families (n=10) were recruited through genetic consultations at the Centre Leon Berard and Hopital Edouard Herriot. Two Amsterdam +ve families were identified in Turkey.	12	Group 1: Fulfilment of Amsterdam Criteria	3	2 (66.6%)	0	IVSP + HA + Sequencing	[Wang et al., 1997]
			Group 2: "incomplete HNPCC syndrome", in which one of the Amsterdam criteria items was missing	9	3 (33.3%)	1 (11.1%)		

France	Kindreds were selected after genetic consultations at the Centre Leon Berard, Hopital Edouard Herriot, Centre Hospitalier Lyon-Sud, Centre Hospitalier Jean Minjoz and Centre Rene Gauducheau. NB – 17 kindreds were previously described (Wang et al., 1997)	75	Group 1: Fulfilment of Amsterdam Criteria	22	11 (50%)	3 (13.6%)	RNA + DNA based screening strategy, utilising HA, RT-PCR and sequencing	[Wang et al., 1999]
			Group 2: "incomplete HNPCC syndrome", in which one of the Amsterdam criteria items was missing	33	6 (18.2%)	2 (6.1%)		
			Group 3: Kindreds with one case of CRC and at least one case of an extra-colonic tumour belonging to the HNPCC spectrum	8	2 (25%)	2 (25%)		
Holland	Dutch Kindreds (n=30) were recruited from various clinical centres, largely through the Netherlands Foundation for the Detection of Hereditary Tumours. The remainder of the kindreds studied were Italian (n=3) and Danish (n=1) in origin.	34	Fulfilment of Amsterdam Criteria	34	12 (35.3%)	2 (20.6%)	DGGE ⇒ Sequencing	[Vasen et al., 1996] NB – These same results are also included in subsequent papers: Wijnen,J. et al., 1995 and Wijnen et al., 1996

Holland + Norway etc.	The 34 kindreds from previous papers (Vasen et al., 1996) are again included in this analysis. In total, 97 Dutch kindreds were included, largely recruited through the Netherlands Foundation for the Detection of Hereditary Tumours. Other kindreds included were Norwegian (n=23), Italian (n=3), Danish (n=1) and Czech (n=1)	125	Group 1: Fulfilment of Amsterdam Criteria	86	25 (29.1%)	17 (19.8%)	DGGE ⇒ Sequencing	[Wijnen et al., 1997]
			Group 2: Family history of CRC, but at least one of the Amsterdam criteria items was missing	39	1 (2.6%)	2 (5.1%)		

Holland + Norway etc.	Some of these kindreds had been studied previously. Overall, 67 kindreds were recruited through the Netherlands Foundation for the Detection of Hereditary Tumours. Further kindreds from the Netherlands (n=56) and from Norway (n=56) were recruited by clinicians or clinical genetics centres. Other kindreds included were Norwegian (n=23), Italian (n=3), Danish (n=1) and Czech (n=1)	184	Group 1: Fulfilment of Amsterdam Criteria	92	25 (27.2%)	16 (17.4%)	DGGE ⇒ Sequencing	[Wijnen et al., 1998a]
			Group 2: Family history of CRC, but at least one of the Amsterdam criteria items was missing	92	3 (3.3%)	3 (3.3%)		

Holland + Norway etc.	This paper re-examines all samples in which no MMR mutations were detected in previous studies, using a different technique to search for genomic deletions. The families studied were Dutch (n=86) and Norwegian (n=51)	137	Group 1: Fulfilment of Amsterdam Criteria	51	N / A	6 (11.7%)	Southern-blot analysis of genomic DNA	[Wijnen et al., 1998b]
			Group 2: Family history of CRC, but at least one of the Amsterdam criteria items was missing	86	N / A	2 (2.3%)		
Holland + Norway etc.	Families registered with the Netherlands HNPCC registry between January and July 2000 (n=193, or which 116 met Amsterdam criteria I or II); plus suspected HNPCC families from the Clinical Genetic Centre Radium Hospital, Oslo, Norway (n=58)	251	Suspected HNPCC, including families meeting the Amsterdam criteria	251	34 (13.5%)	40 (15.9%)	DGGE ⇒ Sequencing	[Vasen et al., 2001]

Germany	Families with suspected HNPCC	69	Group 1: Fulfilment of Amsterdam Criteria	57	11 (19.3%)	4 (7.0%)	SSCA + HA +PTT (where possible) ⇒ Sequencing	[Lamberti et al., 1999]
			Group 2: Fulfilment of a looser criteria, extended to include extra-colonic tumours	12	0	2 (16.7%)		
Germany	Families with suspected HNPCC	29	Most families included fulfilled the Amsterdam criteria (n=27). Two other samples were included.	29	6 (20.7%)	3 (10.3%)	SSCA + HA ⇒ Sequencing	[Wehner et al., 1997]
France	Families, in which no alteration of MMR genes had been previously detected by classical methods	19	Fulfilment of Amsterdam Criteria (n=13) and partial fulfilment of these criteria (n=6)	19	0	3 (15.8%)	Multiplex PCR	[Charbonnier et al., 2000]
England	Kindreds with clustering of colorectal and/or endometrial cancers in consecutive generations.	10	Family history present, but Amsterdam criteria not fulfilled	10	3 (30%)	3 (30%)	SSCP⇒ Sequencing	[Beck et al., 1997]

England	Kindreds with suspected HNPCC, presenting to Southampton General Hospital, UK	6	Family history present, but Amsterdam criteria fulfilled in only 4 of the 6 families	6	3 (50%)	1 (16.7%)	Sequencing	[Coleman et al., 2001]
England	HNPCC families	17	Fulfilment of Amsterdam Criteria	17	3	5	mRNA analysis ⇒ IVTT ⇒ Sequencing	[Froggatt et al., 1996]
Portugal	Portuguese HNPCC families	20	Kindreds either fulfilled the Amsterdam criteria (n=16) or a modification of the criteria, designed to include those families in which three or more relatives have a tumour within the HNPCC spectrum (n=4)	20	7 (35%)	4 (20%)	PTT + SSCP + HA + DGGE	[Fidalgo et al., 2000]

(iii) Australia

Area of Study ; Recruitment period	Study Population and selection criteria	Total Number	Extent of Family History	Select Number	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
Australia	Families ascertained through three centres; The Royal Melbourne Hospital, The Princess Margaret Hospital for Children, and the John Curtin School of Medical Research	18	Fulfilment of Amsterdam Criteria	18	4 (22.2%)	2 (11.1%)	A combination of RNA-based and DNA based methods	[Kohonen-Corish et al., 1996]
Australia	Families with a history of colorectal cancer	95	Fulfilment of Amsterdam Criteria	33	11 (33.3%)	9 (27.3%)	DGGE⇒ Sequencing	[Scott et al., 2001]
			Fulfilment of Bethesda Criteria	62	6 (9.7%)	6 (9.7%)		

(iv) North America

Area of Study ; Recruitment period	Study Population and selection criteria	Total Number	Extent of Family History	Select Number	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference

USA	Kindreds from the USA (n=26), Finland (n=2) and New Zealand (n=1)	29	Fulfilment of Amsterdam Criteria	29	N / A	10 (34.5%)	Linkage analysis ⇒ IVSP ⇒ Sequencing	[Liu et al., 1994]
USA	Patients with a family history of colorectal and/or endometrial cancer were identified from a consecutive series of CRC patients referred to the Gastrointestinal Cancer Prevention Clinic of the Dept. of Internal Medicine at the University of Michigan	19	Group 1: Fulfilment of Amsterdam Criteria	12	4 33.3%)	2 (16.7%)	IVTT ⇒ Sequencing	[Luce et al., 1995]
			Group 2: Amsterdam criteria not entirely fulfilled	7	0	0		
USA + Germany	Patients with a family history of CRC were identified through the Dept. of Medical Genetics at the Mayo clinic, Minnesota, USA, or through the Dept. of Surgery of the University of Dusseldorf.	39	Group 1: Fulfilment of Amsterdam Criteria	20	4 (20%)	5 (25%)	Sequencing	[Moslein et al., 1996]
			Group 2: Index patient plus at least one other family member with CRC	19	3 (15.8%)	0		

USA (?) + Finland	Kindreds with suspected HNPCC. Origin is not clear, but at least 7 of the kindreds were Finnish	28	Group 1: Fulfilment of Amsterdam Criteria, and linkage previously shown to 3p markers	10	9 (90%)	N / A	RT-PCR ⇒ Sequencing	[Papadopoulos et al., 1994]
			Group 2: Fulfilment of Amsterdam Criteria (kindreds too small for linkage analysis)	18	1 (5.6%)	N / A	IVTT ⇒ Sequencing	
USA	Colorectal cancer kindreds	11	Kindreds did not necessarily meet the criteria for HNPCC	11	N / A	1 (9.1%)	Sequencing	[Swensen et al., 1997]
USA	Families self-referred, or referred by health care providers to a cancer genetics program on the basis of multiple CRC cases, early onset or familial association of CRC with other HNPCC-associated tumours	58	Group 1: Fulfilment of Amsterdam Criteria	28	10 (35.7%)	1 (3.6%)	Sequencing	[Syngal et al., 1999]
			Group 2: Families fulfilling a modified Amsterdam Criteria	11	0	2 (18.2%)		
			Group 3: HNPCC variant – families with a history suggestive of HNPCC, but not fulfilling the above criteria	19	0	3 (15.8%)		

USA	HNPCC pedigrees registered with the Roswell Park Familial Cancer Registry and the Vermont Cancer Centre Familial Cancer Program	32	All but one of the kindreds met the Amsterdam Criteria. In the kindred that did not, all affected individuals were confined to the same generation.	32	5 (15.6%)	3 (9.4%)	SSCP⇒ Sequencing	[Weber et al., 1997]
Canada	Patients were identified through the Familial GI Cancer registry at Mount Sinai Hospital, Toronto. All but one families were of European descent, the other being Chinese.	3	Group 1: Fulfilment of Amsterdam Criteria	14	2	5	RT-PCR + PTT ⇒ Sequencing	[Bapat et al., 1999]
			Group 2: Families fulfilling a modified Amsterdam criteria, referred to as the Mount Sinai Hospital Criteria.	19	1	4		

(v) Meta-analysis

Area of Study ; Recruitment period	Study Population and selection criteria	Total Number	Extent of Family History	Select Number	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
Various	Data was collected from survey forms mailed to members of the ICG-HNPCC. Data were gathered from eight institutions in seven countries. Amsterdam +ve families were excluded from the analysis, and the famililies included were classified according to the criteria for families with suspected HNPCC, as defined by the ICG-HNPCC at the 8th annual meeting in Buffalo, USA	123	Criteria I: at least two first-degree relatives affected with colorectal cancer with at least one of the following: development of multiple colorectal tumors including adenomatous polyp, at least one colorectal cancer case diagnosed before the age of 50, and occurrence of a hereditary nonpolyposis colorectal cancer extracolonic cancer (endometrium, urinary tract, small intestine, stomach, hepatobiliary system, or ovary) in family members.	67	12 (17.9%)	7 / 66 (10.6%)	Various	[Park et al., 1999b]
			Criteria II: one colorectal cancer patient with at least one of the following: early age of onset (<40 years); endometrial, urinary tract, or small intestine cancer in the index patient or a sibling (one aged <50 years); and two siblings with other integral hereditary nonpolyposis colorectal cancer extracolonic cancers (one aged <50 years).	56	4 (7.1%)	1 (1.8%)		

(b) Mutation Analysis in Patients with MSI +ve Tumours

(i) Asia

Area of Study ; Recruitment period	**Study Population and ascertainment criteria**	**Age Range**	**Total Number**	**Number MSI +ve**	**Criteria for MSI +ve status**	**Number selected for mutation analysis**	**HMLH1 mutation carriers**	**hMSH2 mutation carriers**	**Method**	**Reference**
Hong Kong, 1991 - 1997	Patients with adenocarcinoma removed at colectomy at Queen Mary Hospital, Hong Kong	<46 years old	59	19 (32%)	RER phenotype at >40% of loci analysed	15	1 (7%)	7 (47%)	IVSP ⇒ sequencing	[Chan et al., 1999]
Japan	Colorectal cancer patients undergoing surgery at the Jichi Medical School. No patients had a family history of CRC in a first degree relative		102	16 (15.7%)	RER evident in at least 1/6 loci	16	0	0	SSCP ⇒ Sequencing	[Senba et al., 1998]
Japan, 1992-1997	CRC patients over a five year period at the Cancer Institute Hospital		129	N / A	RER phenotype in at least 2 of 4 loci	8	1 (12.5%)	N / A	Automated 2D DNA typing system	[Sasaki et al., 1997]

Japan 1980-1995	Patients treated at Hiroshima University School of Medicine, who fulfilled the Japanese registry's clinical diagnostic criteria for HNPCC. Five of these fulfilled the Amsterdam criteria	29	11 (37.%)	RER phenotype in >6 of 12 loci	11	4 (36.4%)	2 (18.2%)	SSCP ⇒ Sequencing	[Nakahara et al., 1997]
Japan	Sporadic CRC cases undergoing surgery at Nihon University School of Medicine, Tokyo. No cases of HNPCC or FAP were included	110	31 (28.2%)	RER phenotype in at least 1 of 8 loci	31	0	0	SSCP ⇒ Sequencing	[Abe and Masuda, 2000]

(ii) Europe

Area of Study ; Recruitment period	Study Population and ascertainment criteria	Age Range	Total Number	Number MSI +ve	Criteria for MSI +ve status	Number selected for mutation analysis	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
Scotland 1970-1993	Index patients identified from the Scottish National Cancer Registry. Patients referred specifically because they fulfilled HNPCC criteria were excluded.	<35 years old	27	13 (48.1%)	RER phenotype in at least 50% of at least 4 loci	13	1 (7.7%)	5 (38.5%)	IVSP ⇒ SSCP ⇒ Sequencing	[Dunlop et al., 1997]
Poland	Late onset sporadic CRC cases, with no family history of HNPCC associated cancers, and without synchronous or metachronous cancers.	>40 years old	43	4 (9.3%)	RER phenotype in at least 2 loci from a panel of 5, or in at least 3 of 10 loci	4	0	0	Sequencing	[Debniak et al., 2000]

Slovenia, 1996-1998	Patients diagnosed with CRC from clinics all over Slovenia		300	29 (MSI-H)	RER phenotype in at least > 40% of up to 12 loci	29	3 (10.3%)	1 (3.4%)	PCR + single / double conformational analysis ⇒ Sequencing	[Ravnik-Glavac et al., 2000]
Germany	Group A: some relatives affected by tumours of the HNPCC spectrum, with out meeting the Amsterdam Criteria	<50 years old	45	26 (57.8%)	RER phenotype in at least > 40% of up to 10 loci	17	4 (23.5%)	1 (5.9%)	SSCA + HA +PTT (where possible) ⇒ Sequencing	[Lamberti et al., 1999]
	Group B: Apparently sporadic colorectal cancer		46	16 (34.8%)		10	2 (20%)	1 (10%)		
Germany / Czech Republic	Index cases meeting the Bethesda guidelines, recruited from the Department of Visceral, Thoracic and Vascular Surgery, University of Dresden and from other departments in Germany and the Czech Republic.		72	38 (52.8%)	RER phenotype at >30% of at least five markers assessed	38	8 (21%)	9 (23.7%)	Sequencing	[Pistorius et al., 2000]

Finland, May 1994 – April 1996	Consecutive cases of sporadic colorectal cancer treated in nine regional hospitals in SE Finland		509	63 (12.4%)	RER phenotype in at least 2/7 loci, or 1 of 7 plus at least 1 from an additional panel	63	9* (14.3%) *Mostly founder mutations	1 (1.6%)	Founder mutation analysis ⇒ Sequencing	[Aaltonen et al., 1998]
Finland, March 1996 – June 1998	Consecutive cases of sporadic colorectal cancer treated in nine regional hospitals in SE Finland	29 – 91 years, mean age = 67	535	66 (12.3%)	DNA was studied for MSI using the BAT26 and TGF-βRII poly-A markers	66	17* (26%) *Mostly founder mutations	1 (1.5%)	Founder mutation analysis ⇒ DGGE ⇒ Sequencing	[Salovaara et al., 2000]
Finland, 1994-1998	Colorectal adenoma specimens collected at colonoscopy or surgery in nine large regional hospitals in SE Finland.	23 - 90 years old, mean age = 66	378	6 (1.6%)	DNA was studied for MSI using the BAT26 and TGF-βRII poly-A markers	6	5 (83.3%)	0	Founder mutation analysis ⇒ Sequencing	[Loukola et al., 1999]

Finland	Colorectal tumour samples that had previously been shown to be unstable at 1 or 2 of 6-14 loci, but had not met the criteria for RER positivity		49	15	RER phenotype in at 1 or more of an additional six markers	11 ‘mild’ RER tumour specimens	0	0	RT-PCR ⇒ IVSP ⇒ Sequencing	[Percesepe et al., 1998]
Finland	Tumour DNA was from primary colorectal carcinomas previously found to have an RER+ve phenotype	36 – 89 years mean age = 70	N / A	33	N / A	33	1 (3%)	1 (3%)	2-D Gel Electrophoresis	[Wu et al., 1997]
Sweden, 1996-1998	Consecutive pre-operative biopsy specimens from rectal cancers in patients referred to the Dept. of Oncology, University Hospital, Lund, Sweden	24 - 92 years median age = 65	165	3 (1.8%)	RER phenotype in at least 1 of at least 4 loci (always including BAT25, BAT26 and BAT40)	3	1 (33.3%)	1 (33.3%)	DGGE ⇒ Sequencing	[Nilbert et al., 1999]

Sweden	Kindreds meeting the extended Amsterdam criteria for HNPCC (n=14), plus kindreds in which the proband presented at an early age with metachronous colorectal / endometrial cancer (n=2). Origin of the kindreds is not given; most were Swedish although at least one was from the Czech republic, and one from Iran.		N / A	16	According to Boland et al., (1998)	16	5 (31.3%)	2 (12.5%)	DGGE ⇒ Sequencing	[Planck et al., 1999]
Portugal	Patients presenting with apparently sporadic colorectal cancer. Cases were excluded if they matched the criteria for a diagnosis of HNPCC, FAP, IBD or if they had undergone preoperative radio / chemotherapy.	34 – 83 years mean age =64	62	9 (14.5%)	RER phenotype in at least 2/7 poly(CA) loci	8	2 (25%)	0	DGGE ⇒ Sequencing	[Cravo et al., 1999]

Italy	Italian colorectal cancer patients prospectively ascertained through the Modena CRC Registry.	336	28 (8.3%)	MSI in >30% of markers	12 **NB**: eight were randomly chosen, four were chosen on the basis of clinical features	0	1 (8.3%)	SSCP ⇒ Sequencing **NB**: Some sequenced directly	[Percesepe et al., 2001]

(iii) North America

Area of Study ; Recruitment period	Study Population and ascertainment criteria	Age Range	Total Number	Number MSI +ve	Criteria for MSI +ve status	Number selected for mutation analysis	HMLH1 mutation carriers	hMSH2 mutation carriers	Method	Reference
USA + Scotland	Scotland: A subset of 115 CRC registrations between 1970 and 1993, that met practical criteria for analysis (n=17) USA: (i) Patients with stage II or III CRC undergoing curative surgical resections at the Johns Hopkins Hospital between 1986 and 1990 (n=145) (ii) Randomly selected patients in whom surgery was performed between 1978 and 1985 (n=65) All patients were excluded if they met the Amsterdam criteria for HNPCC, or had evidence of FAP or IBD	Scotland: <30 years old USA: (i) unknown (ii) <50 years old	189 (38 of the 227 samples were not of adequate quality)	37 (19.6%)	RER phenotype in at least 2 of 4 or 5 loci	12	2 (16.7%)	3 (25%)	RT-PCR ⇒ IVSP ⇒ Sequencing	[Liu et al., 1995a]

USA	Consecutive cases of sporadic colorectal cancer, treated at the Johns Hopkins Hospital (1984-1990)	181	24 (13.3%)	N / A	10	0	1 (10%)	RT-PCR ⇒ IVSP ⇒ Sequencing	[Liu et al., 1995b]
USA + New Zealand + Europe	Kindreds meeting the Amsterdam criteria for HNPCC were included in the study. The origin of the kindreds were USA (n=50), New Zealand (n=12) and Europe (n=12) NB: 19 of the 31 mutation+ve patients had been identified through previous studies	74	68 (91.9%)	RER phenotype in at least 2 of 4 or more loci	48	16 (33.3%)	15 (31.3%)	RT-PCR ⇒ IVSP ⇒ Sequencing	[Liu et al., 1996]
USA	Patients with MSI +ve colorectal tumours identified by a previous study, classed as sporadic (n=7) CRC cases	N / A	7	N / A	7	1 (14.3%)	0	Sequencing	[Moslein et al., 1996]

USA	Colorectal cancer patients were recruited through the Washington University School of Medicine, St. Louis, Missouri	38-83 years mean age = 65.6	61	13 (21.3%)	RER phenotype in at least 2 of 7 loci	12	1 (8.3%)	0	RT-PCR + SSCP ⇒ Sequencing	[Herfarth et al., 1997]
USA	Unselected prospective series of patients presenting to the Mayo clinic, Minnesota, between December 1995 and April 1997, and consenting to participate	29–91 years, mean age = 69	257	51 (19.8%)	Instability evident in more than 30% of seven markers analysed	51	4 (7.8%)	3 (5.8%)	Sequencing	[Cunningham et al., 2001]
USA	Colon cancer patients from Utah and California, originally enrolled as part of a wider epidemiological study. Patients with rectal cancer were excluded.	30-79 years	1066	171 (16.0%)	MSI in >30% of 10 tetranucleotide repeats, or instability of BAT-26 or TGF-βRII	130	5 (3.8%)	3 (2.3%)	Sequencing	[Samowitz et al., 2001]

(c) Mutation Analysis in Patients with early onset colorectal cancer

Area of Study ; Recruitment period	**Study Population and selection criteria**	**Age**	**Number selected for mutation analysis**	**HMLH1 mutation carriers**	**hMSH2 mutation carriers**	**Method**	**Reference**
Scotland	Scottish sporadic CRC patients diagnosed at <30 years, identified retrospectively from cancer registrations since 1970	<30 years old	50	7 (14%)	7 (14%)	Sequencing plus complementary IVSP	[Farrington et al., 1998]
England	CRC cases in young patients with no family history of CRC	<45 years old	50	2 (4%)	1 (2%)	SSCP⇒ Sequencing	[Tomlinson et al., 1997]
France	Caucasian CRC patients in a clinic-based population, selected solely on the basis of age at onset of CRC.	<50 years old	7	0	0	SSCP⇒ Sequencing	[Dieumegard et al., 2000]

France	Patients recruited through genetic consultations at the Centre Leon Berard and Hopital Edouard Herriot.	<50 years old	7	0	0	IVSP + HA + Sequencing	[Wang et al., 1997]
France	Patients selected after genetic consultations at the Centre Leon Berard, Hopital Edouard Herriot, Centre Hospitalier Lyon-Sud, Centre Hospitalier Jean Minjoz and Centre Rene Gauducheau.	<50 years old	12	0	0	RNA + DNA based screening strategy, utilising HA, RT-PCR and sequencing	[Wang et al., 1999] NB – Some patients may have been described previously (Wang et al., 1997)
Italy	Patients were recruited “from various surgical and clinical units”. Family history was not used as an entry criterion.	<50 years old	54	5 (9.2%)	4 (7.4%)	SSCP + PTT ⇒ Sequencing	[Montera et al., 2000]

Italy	Patients without a family history suggestive of hereditary CRC, treated at the Centro di Riferimento Oncologico, Aviano, Italy (~1995-1999)	<45 years old	38	1 (2.6%)	2 (5.3%)	SSCP⇒ Sequencing	[Fornasarig et al., 2000]
Korea	Data on early-onset CRC without family history were collected through the Dept. of Surgery, Seoul National University Hospital.	<50 years old	22	0	1 (4.5%)	SSCP⇒ Sequencing	[Han et al., 1996]
Korea	Data on early-onset CRC cases without family history were collected through the Dept. of Surgery, Seoul National University Hospital.	<50 years old	45	0	1 (2.2%)	SSCP⇒ Sequencing	[Yuan et al., 1998] NB Continuation of above study

USA	Patients without a family history fulfilling the strict, or the modified, Amsterdam criteria	<40 years old	12	1 (8.3%)	1 (8.3%)	Sequencing	[Syngal et al., 1999]
USA	African Americans enrolled with the Roswell Park Family Cancer Registry	<50 years old	10	1 (10%)	1 (10%)	SSCP⇒ Sequencing	[Weber et al., 1999]

Abbreviations

CRC = Colorectal Cancer, DGGE = Denaturing Grade Gel Electrophoresis, FAP = Familial Adenomatous Polyposis, HA = Heteroduplex Analysis, HNPCC = Hereditary Non-Polyposis Colorectal Cancer, IBD = Inflammatory Bowel Disease, ICG HNPCC = International Collaborative Group on HNPCC, IVTT = In Vitro Transcription-Translation, IVSP = In Vitro Synthesised Protein assay, MSI = Microsatellite Instability, PCR = Polymerase Chain Reaction, PTT = Protein Truncation Test, RER = Replication Error, RT-PCR = Reverse Transcription Polymerase Chain Reaction, SSCP = Single Stranded Conformational Polymorphism

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